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Different Drug Protocols for Rheumatoid Arthritis: An Exhaustive Review

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ABSTRACT

The chronic systemic autoimmune illness known as rheumatoid arthritis (RA) is typified by bone erosion, cartilage deterioration, and persistent synovitis. Its complicated immunopathogenesis includes environmental triggers, genetic susceptibility, and dysregulated cytokine networks. Results have changed with the advent of treat to target tactics and a growing arsenal of disease-modifying antirheumatic medications (DMARDs). This review integrates information from significant research and guidelines to examine new and existing pharmacologic treatments for RA. Because of its effectiveness, affordability, and good long-term safety, methotrexate continues to be the cornerstone of conventional synthetic DMARD treatment. Leflunomide, hydroxychloroquine, and sulfasalazine are substitutes or combinations of these medications, especially in environments with low resources. T cell co-stimulation blockers and B cell depleting antibodies provide choices for refractory patients, whereas tumor necrosis factor inhibitors and interleukin 6 receptor antagonists lead the biologic DMARD class, which targets certain cytokines or cells. Targeted synthetic DMARDs, primarily Janus kinase (JAK) inhibitors like tofacitinib, baricitinib, and upadacitinib, offer quick onset and oral administration; nevertheless, because of the hazards of infection, thrombosis, and cardiovascular disease, they should be closely monitored. Analgesics, short-term corticosteroids, and non-steroidal anti-inflammatory medications are examples of bridge therapy that provide symptomatic relief but do not stop the course of the disease. Exercise, rehabilitation, nutrition, and patient education are examples of non-pharmacologic therapies that enhance quality of life and supplement medication. The review shows a flowchart for an evidence-based management strategy and provides tables that summarize pharmacological mechanisms, dosage, and side effects. The focus of future research will be on cell-based medicines, biosimilars, selective kinase inhibitors, and precision medicine. All things considered, the study emphasizes the need for customized treatment regimens that strike a balance between patient preferences, safety, and efficacy in order to achieve long-lasting remission and enhanced functional results.

KEYWORDS: rheumatoid arthritis, disease modifying antirheumatic drugs, bridge therapies, non pharmacological treatments.

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INTRODUCTION

The chronic, systemic autoimmune illness known as RA is typified by ongoing synovial inflammation that results in bone erosion, cartilage degradation, and disability. It is linked to significant morbidity and early death and affects around 0.5% to 1% of the world's population [1]. Genetic susceptibility (HLA-DRB1 shared epitope alleles), environmental variables (smoking, changes in the microbiota), and dysregulated immune responses all contribute to the onset and spread of illness, even if the underlying triggers are still unknown [2]. The treatment landscape has seen significant transformation in the last three decades, with the early introduction of DMARDs, treat-to-target techniques, biologic medicines, and tailored synthetic therapies revolutionizing results. The immunopathogenesis of RA is summarized in this review, which also offers a thorough examination of pharmacological regimens, including bridge therapies, supportive measures, and new treatments, as well as conventional synthetic (cs) DMARDs, biologic DMARDs (bDMARDs), and targeted synthetic (ts) DMARDs [3]. Tables and illustrations are used to help with understanding, and the text concentrates on evidence-based guidelines, mechanisms of action, dose, monitoring, and safety profiles.

The approved medications used to treat RA may be roughly divided into a number of categories, which is depicted in the Figure 1.

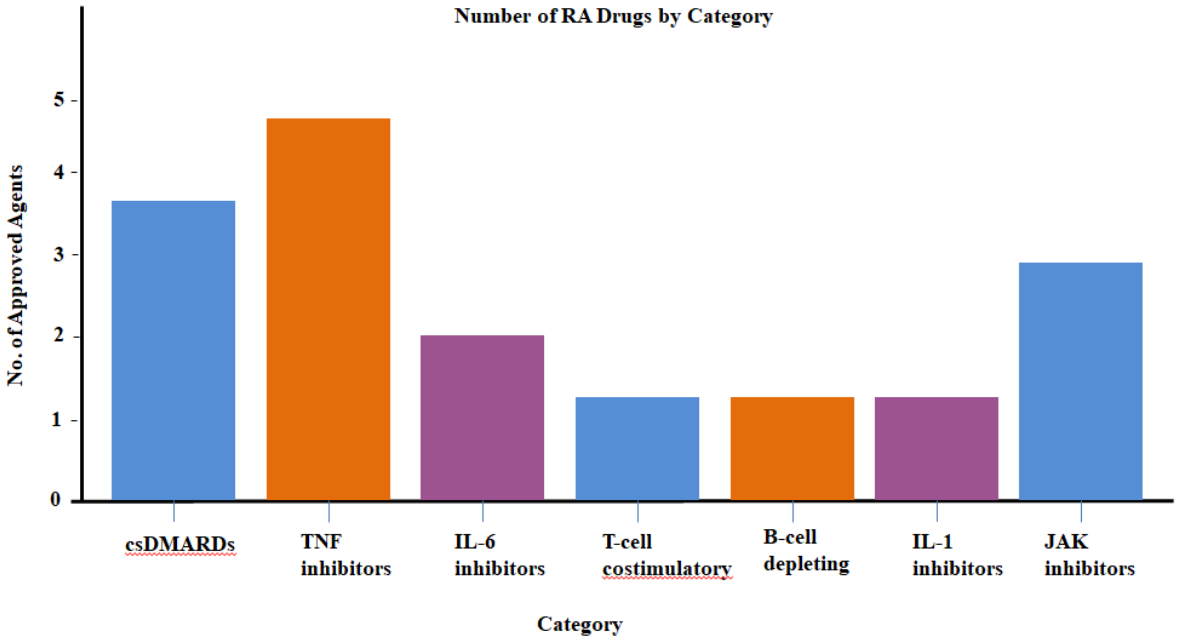

Figure 1 – Number of RA drugs by category [4].

The number of drugs spanning TNF inhibitors, IL-6 inhibitors, B-cell depletion, T-cell co-stimulation modulators, csDMARDs, IL-1 inhibitors, and JAK inhibitors is summarized in the bar chart. With five drugs, TNF inhibitors are the most prominent category; B-cell depletion and T-cell co-stimulation modulators each have one agent. This demonstrates how the biologic era has seen a substantial expansion of the treatment arsenal [4].

Immunopathogenesis of Rheumatoid Arthritis

An immune-mediated inflammatory illness is the best way to describe RA. The synovium is a thin, fragile lining found in normal joints that creates lubricants and maintains cartilage feeding. The sub-intimal space is severely invaded with T and B lymphocytes, macrophages, mast cells, and osteoclast precursors in RA, and the lining becomes hypertrophic (8–10 cell layers). Pro-inflammatory cytokines that promote synovial inflammation, pannus development, and matrix breakdown are released by these cells and include interleukin-1 (IL-1), IL-6, IL-17, and tumor necrosis factor-α (TNF-α). Invasion and erosion of bone and cartilage are caused by the hypertrophied synovium [5]. Cartilage is broken down by proteolytic enzymes (collagenase, stromelysin) and reactive oxygen species produced by chondrocytes and synovial fibroblasts [6]. Bone resorption results from osteoclast differentiation in response to cytokines and the receptor activator of nuclear factor-κB ligand (RANK-L). About 30% of the hereditary risk for RA is due to genetic factors like the shared epitope of HLA-DR4, but environmental triggers including smoking, periodontal disease, and mucosal infections encourage the creation of citrullinated peptides and anti-citrullinated protein antibodies [7].

Treat-to-Target Strategy and Therapeutic Goals

The treat-to-target (T2T) strategy serves as the foundation for contemporary RA therapy. In order to achieve low disease activity or remission, this calls for early diagnosis, timely DMARD medication beginning, and regular monitoring (every one to three months) with treatment adjustments. The 2021 American College of Rheumatology (ACR) guideline conditionally recommends methotrexate over leflunomide and strongly recommends it over hydroxychloroquine or sulfasalazine for DMARD-naïve patients with moderate-to-high disease activity [8]. Additionally, the recommendation cautions against long-term glucocorticoid use and conditionally favors commencing with csDMARDs instead of a biologic or targeted synthetic DMARD [9]. These ideas are summarized by the Arthritis Foundation, which emphasizes the use of methotrexate as first-line therapy, the use of biologics or Janus kinase (JAK) inhibitors only when methotrexate has failed, and the avoidance of long-term corticosteroid usage [9]. Figure 2 illustrates a treat-to-target approach that uses csDMARDs first, then bDMARDs or tsDMARDs, and then supplementary therapy.

Conventional Synthetic DMARDs (csDMARDs)

Oral small-molecule drugs known as csDMARDs are reasonably priced and affect the immune system. Methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine are among the medications that continue to be used as first-line treatment for RA [10]. Their mechanisms, dosage, and main side effects are presented in Table 1.

Table 1 – csDMARDs

Agent	Mechanism of action	Typical dosing & route	Key adverse effects
Methotrexate	Folic acid antagonist; inhibits dihydrofolate reductase and increases adenosine [11].	15–25 mg/week orally or subcutaneously with folic acid	Gastrointestinal upset, liver enzyme elevation, cytopenias, teratogenicity, interstitial pneumonitis.
Sulfasalazine	Converted to sulfapyridine and 5-aminosalicylic acid; modulates prostaglandin synthesis and immune function [12].	500 mg/day escalating to 2–3 g/day orally	Nausea, rash, reversible oligospermia, agranulocytosis, hepatotoxicity.
Leflunomide	Inhibits dihydro-orotate dehydrogenase, blocking pyrimidine synthesis [13].	Loading 100 mg/day for 3 days then 20 mg/day orally	Diarrhea, alopecia, hypertension, hepatotoxicity, teratogenicity.
Hydroxychloroquine	Inhibits toll-like receptor signalling and antigen presentation [14].	200–400 mg/day orally	Retinal toxicity, gastrointestinal upset, skin hyperpigmentation.

Methotrexate

Methotrexate, an analogue of folic acid, decreases purine and pyrimidine production and, therefore, cell proliferation by blocking dihydrofolate reductase and thymidylate synthase. Additionally, extracellular adenosine, which has anti-inflammatory properties, is increased. Weekly dosages of 15–25 mg of methotrexate are given orally or subcutaneously, along with folic acid supplements. It has a favorable cost-benefit ratio and is highly recommended as a first-line treatment [15]. Long-term usage necessitates monitoring of liver function, renal function, and total blood count; common side effects include gastrointestinal distress, stomatitis, increase of liver enzymes, and cytopenias. Pregnancy, severe renal impairment, chronic liver disease, and active infections are among the contraindications. Interstitial pneumonitis, or pulmonary poisoning, is uncommon yet dangerous [16].

Sulfasalazine

Sulfapyridine and 5-aminosalicylic acid are the products of sulfasalazine metabolism. Inhibiting prostaglandin formation and modifying T- and B-cell responses are two of its anti-inflammatory mechanisms. The dosage is titrated up to 2-3 g/day after starting at 500 mg/day. Agranulocytosis and hepatotoxicity are uncommon side effects, along with gastrointestinal distress, dermatitis, and reversible oligospermia. It is advised to have routine liver function and total blood count testing. Conditionally, sulfasalazine is taken either alone or in conjunction with methotrexate [17].

Leflunomide

The active metabolite, A77 1726, which is produced when leflunomide is metabolized, inhibits dihydroorotate dehydrogenase, which reduces pyrimidine production and stops T-cell proliferation. It is taken orally for three days at a loading dosage of 100 mg per day, and then for maintenance at 20 mg per day. Common adverse effects include hepatotoxicity, alopecia, diarrhea, and hypertension. Due to its lengthy half-life of two weeks, cholestyramine wash-out could be required prior to conception. Effective contraception is necessary since leflunomide is teratogenic. For DMARD-naïve individuals, the ACR guideline conditionally suggests methotrexate over leflunomide [18].

Hydroxychloroquine

The antimalarial drug hydroxychloroquine builds up in lysosomes and prevents the synthesis of cytokines, antigen presentation, and toll-like receptor signaling. 200–400 mg are taken orally each day. Although it is less successful in preventing structural damage, it has a favorable safety profile and is typically used in combination therapy or for moderate diseases. The main issue is retinal toxicity, which calls for baseline and yearly ophthalmologic exams. Other adverse effects include skin discoloration and disturbed stomach. ACR guidelines state that in patients with active RA, methotrexate is better than hydroxychloroquine [19].

Combination csDMARD therapy

The effectiveness of combination csDMARDs, including methotrexate with hydroxychloroquine and sulfasalazine, may be increased. Triple treatment is advised prior to shifting to bDMARDs or tsDMARDs, since it has been demonstrated in certain trials to be non-inferior to biologics. Comorbidities, patient desire, and the severity of the disease all influence the decision [20].

Biologic DMARDs (bDMARDs)

bDMARDs are proteins that have been designed to target particular cytokines or chemicals found on the cell surface. Although they are costly and raise the risk of infection, they are quite effective in lowering disease activity and structural damage when administered by injection or infusion. They are typically utilized when csDMARDs don't work as intended [21]. Key properties, agents, and bDMARD classes are summarized in Table 2.

Table 2 – Biologic DMARDs (bDMARDs)

Class & agents	Target & mechanism	Administration	Key considerations
TNF inhibitors: infliximab, adalimumab,	Neutralise TNF-α, preventing activation	Intravenous (infliximab), subcutaneous (others); dosing	Screen for latent TB and hepatitis; risk of serious infections, injection

Class & agents	Target & mechanism	Administration	Key considerations
etanercept, golimumab, certolizumab pegol	of NF-κB signalling [22].	varies (e.g., adalimumab 40 mg every 2 weeks) [23].	reactions and rare demyelinating disease.
IL-6 receptor antagonists: tocilizumab, sarilumab	Block IL-6R, suppressing cytokine signalling	Intravenous every 4 weeks or subcutaneous every 1–2 weeks	Monitor neutrophils, liver enzymes and lipids; risk of infections and GI perforation.
IL-1 receptor antagonist: anakinra	Competitive inhibition of IL-1 receptor [24].	Daily subcutaneous injection [14].	Less effective than other biologics; injection-site reactions and neutropenia.
T-cell co-stimulation modulator: abatacept	Binds CD80/CD86 to inhibit T-cell activation [25].	Intravenous at 0, 2 and 4 weeks then every 4 weeks or weekly subcutaneous [15].	Useful in patients with inadequate response to TNF inhibitors; avoid in severe COPD.
B-cell depleting therapy: rituximab	Anti-CD20 monoclonal antibody depleting B cells [16].	Two intravenous infusions 2 weeks apart, repeated every 6–12 months [26].	Infusion reactions; risk of hepatitis B reactivation and progressive multifocal leukoencephalopathy.

Tumour-Necrosis Factor inhibitors

One important cytokine that promotes joint degradation and synovial inflammation is TNF-α. For RA, five anti-TNF medications have been approved: certolizumab pegol, etanercept (TNF receptor–Fc fusion protein), adalimumab (fully human monoclonal antibody), infliximab (chimeric monoclonal antibody), and golimumab [27]. By binding TNF-α and preventing its interaction with TNF receptors, these medicines impede the activation of NF-κB downstream [28]. They lessen radiographic progression and disease activity, and their combination with methotrexate increases their effectiveness. Injection site responses, infusion reactions, opportunistic infections (fungi, TB), recurrence of hepatitis B, demyelinating illness, congestive heart failure, and uncommon lupus-like condition are among the side effects. Prior to commencement, a latent TB and hepatitis screening as well as current vaccines are required. Biosimilars, such as adalimumab-atto and adalimumab-afzb, offer affordable substitutes [29].

Interleukin-6 receptor antagonists

As the primary cause of synovial inflammation, acute phase response, and systemic symptoms, IL-6 is essential to the pathophysiology of RA. Monoclonal antibodies that inhibit the IL-6 receptor (IL-6R) include tocilizumab and sarilumab. Tocilizumab works well as a monotherapy or in combination with methotrexate, and it can be administered intravenously every 4 weeks or subcutaneously every 2 weeks [30]. Every two weeks, sarilumab is injected subcutaneously. Neutropenia, increased liver enzymes, hyperlipidemia, and the possibility of gastrointestinal perforation are among the side effects. It is necessary to regularly check liver function tests and blood counts. Despite csDMARDs or TNF inhibitors, the American College of Radiation Therapy (ACR) advises IL-6 inhibitors for patients with moderate-to-high disease activity [31].

Interleukin-1 receptor antagonist

The recombinant IL-1 receptor antagonist Anakinra is injected subcutaneously once a day. IL-1 promotes osteoclast activation and chondrocyte enzyme synthesis, which damages bone and cartilage. Although Anakinra reduces symptoms, its usage is limited since it needs daily dose and is less effective than other biologics. Patients who are contraindicated for other bDMARDs may be given consideration [32].

T-cell co-stimulation modulator

A fusion protein called Abatacept is made up of IgG1 Fc and the extracellular domain of cytotoxic T lymphocyte antigen 4 (CTLA-4). It inhibits co-stimulatory signaling via CD28 on T cells by binding to CD80/CD86 on antigen-presenting cells, which lowers T-cell activation. Abatacept is given subcutaneously once a week or intravenously at 0, 2, and 4 weeks, and then every 4 weeks. It has a favorable safety profile and is advised for individuals who do not respond well to TNF inhibitors or csDMARDs. It is comparatively contraindicated in cases of severe chronic obstructive pulmonary disease; adverse effects include infusion responses and an elevated risk of infections [33].

B-cell depleting therapy

A chimeric monoclonal antibody called Rituximab targets B cells' CD20. Through complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity, it destroys B cells. Every six to twelve months, rituximab is given as two intravenous infusions spaced two weeks apart [16]. It works well for seropositive RA and is recommended for people with moderate-to-severe RA who do not respond well to TNF inhibitors. Hepatitis B reactivation, hypogammaglobulinemia, infusion reactions, and progressive multifocal leukoencephalopathy are among the side effects (rare). Steroid and antihistamine pre-medication lowers infusion responses [34].

Other biologics

B-cell activating factor inhibitors like Belimumab and medications that target the IL-17 or IL-12/23 pathways are used to treat other inflammatory illnesses but are not licensed for RA. Potential targets for future biologics might include IL-17A, granulocyte-macrophage colony-stimulating factor (GM-CSF), and other cytokines [35].

Targeted Synthetic DMARDs (tsDMARDs)
Small-molecule inhibitors known as tsDMARDs target intracellular signaling pathways. The cytokine receptors for GM-CSF, IL-6, IL-2, and IL-15 send signals to the JAK–signal transducer and activator of transcription (STAT) pathway. These medications block a variety of cytokine pathways by blocking JAK enzymes. Oral JAK inhibitors have a quick onset. Approved JAK inhibitors are summarized in Table 3 [36].

Table 3 – tsDMARDs / JAK inhibitors

Agent	JAK selectivity	Typical dosing	Notable features
Tofacitinib	JAK1/3 > JAK2	5 mg twice daily or 11 mg extended-release once daily	First approved JAK inhibitor; boxed warning for serious cardiovascular events and malignancy; monitor lipids and blood counts [37].
Baricitinib	JAK1/2	2–4 mg once daily	Comparable efficacy to adalimumab; adjust dose in renal impairment; risk of infection and thrombosis
Upadacitinib	JAK1	15 mg once daily	Approved for RA in 2019 [17]; rapid onset; similar safety concerns; used after inadequate response to methotrexate.
Filgotinib (EU/Japan)	JAK1	100–200 mg once daily	Approved in Japan and EU; not FDA-approved; under study for RA and Crohn's disease [38].
Peficitinib (Japan)	Pan-JAK	100–150 mg once daily	Approved in Japan; global availability limited; long-term safety data needed [39].

Tofacitinib
JAK1 and JAK3 are inhibited by Tofacitinib, but JAK2 is somewhat active. In 2012, it was authorized as the first JAK inhibitor for RA. 5 mg twice daily or 11 mg extended-release once daily is the typical dosage. It slows down structural deterioration and lessens RA symptoms. Infection, lymphopenia, higher transaminases, lipid elevation, and an increased risk of herpes zoster are among the side effects. A boxed warning for significant heart-related events and malignancy was given by the U.S. FDA in 2021. It necessitates a thorough risk evaluation and should be administered following an insufficient response to TNF inhibitors [40].

Baricitinib
Baricitinib inhibits JAK1 and JAK2 selectively. For moderate-to-severe RA, it was approved by the FDA in 2018 and the EMA in 2017. It is taken orally once daily in doses of 2 or 4 mg. It has demonstrated better structural results and effectiveness on par with adalimumab. Thrombosis, lipid problems, and infection are among the risks. In cases of renal impairment, dose modification is required [41].

Upadacitinib
Upadacitinib is permitted to treat RA, psoriatic arthritis, atopic dermatitis, and ulcerative colitis by specifically inhibiting JAK1. 15 mg once daily is the usual dosage for RA; some disorders call for a greater dose of 30 mg. It offers quick symptom relief and inhibits radiography, but it also has comparable safety risks. The FDA authorized upadacitinib for moderate-to-severe RA in August 2019 [42].

Filgotinib, Peficitinib and other JAK inhibitors
The JAK1 inhibitor filgotinib and the pan-JAK inhibitor peficitinib are approved in the EU and Japan, although they are not commonly accessible. A thorough analysis of JAK inhibitors points out that filgotinib was approved in Japan in 2020, whereas peficitinib had previously received approval in Japan and fedratinib and upadacitinib were approved in 2019 [18]. RA is being studied for delgocitinib and other medications that are licensed for dermatological disorders. Due to safety concerns (malignancy, thrombosis), general usage has been limited [43].

Bridge and Symptomatic Therapies
Patients frequently need analgesic and anti-inflammatory drugs as they wait for flare-ups or for DMARDs to start working. These bridging treatments relieve symptoms but do not change the course of the disease.

NSAIDs, or non-steroidal anti-inflammatory drugs
Cyclo-oxygenase (COX) enzymes are inhibited by NSAIDs, which lowers prostaglandin production and has analgesic and anti-inflammatory properties. Among the options are COX-2-selective inhibitors (celecoxib) and conventional NSAIDs (ibuprofen, naproxen, and diclofenac). NSAIDs reduce pain and stiffness, but they don't impede the course of the condition, according to the NHS [44]. Cardiovascular risk, renal impairment, and stomach ulcers are typical side effects. In high-risk individuals, they are frequently used in conjunction with proton-pump inhibitors and should be administered at the lowest effective dose.

Analgesics and Adjuncts
Paracetamol and other simple analgesics can be used to manage pain [45]. Drugs like duloxetine or gabapentinoids may be recommended for neuropathic pain or fibromyalgia components. For localized pain, topical NSAIDs and capsaicin are viable choices.

Glucocorticoids

Glucocorticoids have strong immunosuppressive and anti-inflammatory properties. Prednisolone is frequently used as a temporary fix when beginning or modifying DMARDs since it can quickly decrease synovitis. Triamcinolone injections used intra-articularly offer local relief. Adverse consequences such weight gain, osteoporosis, diabetes, hypertension, adrenal suppression, and infection risk make long-term systemic steroid usage undesirable [46]. Chronic glucocorticoid treatment should be avoided or minimized, according to the ACR recommendation [8].

Non-pharmacologic and Supportive Interventions

A comprehensive strategy that takes into account social, emotional, and physical factors is necessary for the best care of RA [47]. Citing intermediate evidence for increased physical function and discomfort, the 2022 ACR guideline on exercise, rehabilitation, and integrative therapies suggests regular exercise over no exercise [48]. The program is customized to the patient's capacities and includes aerobic, resistance, aquatic, and mind-body activities (yoga, tai chi) [34]. To improve function, it is conditionally advised to employ orthoses, physical therapy, occupational therapy, and hand treatment [49]. Individualized attention should be paid to energy conservation, activity pacing, assistive technology, and adapted equipment [50]. Weight management lowers joint load, and diets high in fruits, vegetables, whole grains, and omega-3 fatty acids may have mild anti-inflammatory effects. Quitting smoking is crucial. Stress reduction, patient education, and psychological support are essential. Prior to beginning immunosuppressive treatment, vaccinations against influenza, pneumococcal disease, herpes zoster, and COVID-19 should be maximized [51].

Treatment Algorithm

Figure 2 illustrates an algorithmic method to RA treatment. Methotrexate is started following diagnosis and baseline evaluation (including serology, comorbidities, disease activity score, and patient preferences). Changes may involve moving to another csDMARD or using combination csDMARDs if the goal is not reached in 3–6 months [52]. When moderate-to-high activity persists, a bDMARD or tsDMARD should be added. Each step is accompanied by non-pharmacologic therapy and bridge therapies (NSAIDs, short-term glucocorticoids). Pregnancy status, comorbidity evaluation (e.g., infection risk, cancer, cardiovascular disease), and collaborative decision-making are all factors in treatment decisions [53].

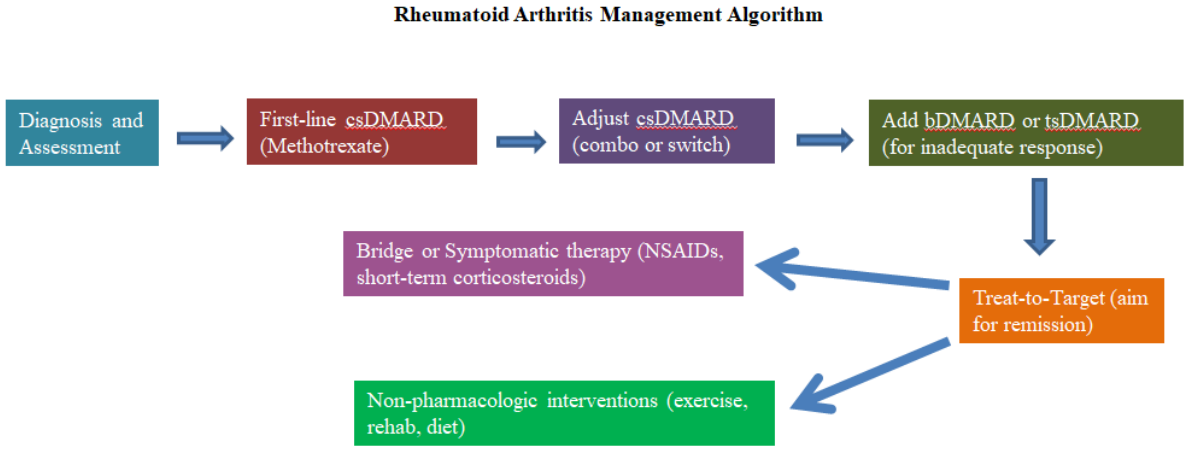

Figure 2 – Rheumatoid Arthritis Management Algorithm [54].

A basic treat-to-target method is shown in Figure 2. Following diagnosis, methotrexate is started as first-line treatment. Insufficient reaction leads to csDMARDs (switch or combination) being adjusted [58]. A bDMARD or tsDMARD is added if remission is not achieved. NSAIDs, short-term glucocorticoids, and non-pharmacologic treatments all offer symptomatic relief. Current ACR guidelines are included in this algorithm [54].

Special Situations

Pregnancy and Lactation

Pregnancy safety and disease management must be balanced when managing RA. Leflunomide and methotrexate must be stopped long before becoming pregnant since they are teratogenic. Sulfasalazine and hydroxychloroquine are usually regarded as safe and can be used indefinitely [55]. Other biologics are discontinued by the second trimester, whereas TNF inhibitors, particularly certolizumab pegol because of its low placental transfer, may be administered until late pregnancy. NSAIDs and glucocorticoids should be used with caution. Methotrexate and leflunomide are contraindicated; hydroxychloroquine, sulfasalazine, and certolizumab are compatible with breastfeeding [56].

Comorbidities and Infection Risk

Immunosuppressive medication and disease-related immunological dysfunction put RA patients at higher risk for infections. Before beginning bDMARDs or tsDMARDs, screening for HIV, hepatitis B and C, and latent TB is required. Inactivated

vaccinations should be given before treatment; once on biologics, live immunizations are often avoided [57]. RA raises the risk of cardiovascular disease; careful management of conventional risk factors, physical activity, and disease suppression lower this risk. Calcium, vitamin D, bisphosphonates, or denosumab, if necessary, should be used to treat and monitor osteoporosis [58].

Emerging and Future Therapies

JAK inhibitors' recent approvals demonstrate the trend toward oral, tailored treatments. For RA, fedratinib, an oral JAK2 inhibitor, is being studied. Anti-GM-CSF antibodies, Bruton's tyrosine kinase (BTK) inhibitors (such as fenebrutinib), and selective tyrosine kinase 2 (TYK2) inhibitors are all being researched. Future approaches include vaccinations that induce tolerance, gene treatments that target cytokine signaling, and cellular therapies (mesenchymal stem cells). Personalized drug selection and tapering may be possible using precision medicine techniques that include genetic, serologic, and imaging biomarkers [59].

DISCUSSION

Oral targeted inhibitors and precision biologics have replaced slow-acting oral medications as the mainstays of RA treatment. Because of its shown effectiveness, long-term safety, and affordability, methotrexate continues to be the mainstay medication. For DMARD-naïve patients with moderate-to-high disease activity, the ACR strongly advises methotrexate monotherapy [60] since research indicates that it lowers mortality and slows radiographic progression. In environments with limited resources, combination csDMARD treatment provides an efficient substitute. However, using csDMARDs alone does not result in remission for around 30–40% of individuals.

The development of bDMARDs, especially TNF inhibitors, transformed the management of RA by bringing about quick and long-lasting disease control. Patients not responding to TNF inhibitors have alternatives with subsequent biologics that target IL-6 or T-cell co-stimulation. Comparable efficacy across bDMARDs is suggested by head-to-head trials; comorbidities (e.g., avoid TNF inhibitors in congestive heart failure), administration method, frequency of dose, and patient preference should all be taken into account when choosing a medication. Because they are less expensive, biosimilars increase access [61].

JAK inhibitors are a paradigm change since they may be taken orally and block a variety of cytokine pathways. Adalimumab's effectiveness is comparable to or better than that of upadacitinib and baricitinib. However, regulatory warnings have been generated by safety signals, such as malignancy, thrombosis, and significant adverse cardiovascular events. Selecting patients and making decisions together are crucial (e.g., avoid in older smokers with cardiovascular risk factors). Newer JAK inhibitors, such as peficitinib and filgotinib, may offer safer and more specific inhibition [62].

Patient education and non-pharmacologic therapies continue to be essential adjuncts. Physical treatment and occupational therapy promote joint preservation and self-management [63], while exercise enhances physical function and lessens discomfort [21]. Comorbidities are lessened by diet, weight management, quitting smoking, and immunization programs. Adherence is increased, cardiovascular risk is decreased, and quality of life is improved with comprehensive care [64].

Future studies will concentrate on durable remission, precision medicine, and early intervention. Biomarkers include genetic markers, imaging (MRI, ultrasound), and serologic profiles (anti-citrullinated protein antibody titers) can predict response and enable tailored treatment [65]. Instead of long-term control, novel targets (GM-CSF, TYK2, BTK) and cell-based therapy provide possible solutions. To assess tapering or cessation techniques in persistent remission, longitudinal studies are required.

CONCLUSION

A complicated autoimmune condition, RA has a varied course. The results of early, vigorous therapy based on treat-to-target principles have changed, allowing many patients to have minimal disease activity or remission. With biologic and tailored synthetic medicines offering effective alternatives for refractory illness, methotrexate continues to be the cornerstone. Prognostic variables, comorbidities, safety profiles, patient preferences, and disease activity must all be carefully taken into account when selecting a medication. Patient education, comorbidity management, and non-pharmacologic therapies are essential. Personalized treatments and a higher standard of living for people with RA are anticipated in the future thanks to continuous innovation.

ABBREVIATIONS

RA: Rheumatoid Arthritis
DMARDs: disease-modifying antirheumatic drugs
JAK: Janus Kinase
csDMARDs: conventional synthetic DMARDs
bDMARDs: biologic DMARDs
tsDMARDs: targeted synthetic DMARDs
TNF-α: Tumour-Necrosis Factor-α
IL-1: Interleukin-1
RANK-L: receptor activator of nuclear factor-κB ligand
T2T: treat-to-target
ACR: American College of Rheumatology
IL6R: Interleukin-6 Receptor
CTLA-4: Cytotoxic T-Lymphocyte Antigen-4
GM-CSF: granulocyte-macrophage colony-stimulating factor
STAT: signal transducer and activator of transcription

COX: Cyclo-oxygenase
TYK2: Tyrosine Kinase 2 inhibitors
BTK: Bruton's tyrosine kinase

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The above data are collected from PubMed, PubChem, Drug Bank, Scopus database.

Authors Contribution
Subarnarekha Maitra and Dibya Sinha: Literature review, writing and editing the draft, figures, and table drawing. Sreemoy Kanti Das, Subhasis Maity and Tathagata Roy: Conceptualization, supervision, proofreading, and administration.

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Conflicts of Interest
The authors declare that there is no conflict of interest.

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